DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

5411 38d

JUN 13 2003

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Rory O'Rierdan
Managing Director
Clonmel Healthcare Ltd.
2nd Floor, Unit 20A
Becket Way
Parkwest Business Park
Dublin 12, Ireland

Dear Mr. O'Rierdan:

During the period February 13 and 14, 2003, Investigator Susan Laska from the Philadelphia District Office conducted an inspection of your firm located at the above address to determine your firm's compliance with the Postmarketing Adverse Drug Experience (PADE) reporting requirements of Section 505(k) of the Federal Food, Drug, and Cosmetic Act ("the Act"), and Title 21, *Code of Federal Regulations* (CFR), Part 314.80.

Based on our review of the inspection report, we conclude that your firm violated Section 301 (e) of the Act because it failed to comply with 21 CFR 314.80 and Section 505 (k)(1) of the Act.

Deviations from the PADE regulations include, but are not limited to the following:

1. Failure to promptly review and submit to the FDA adverse drug experience (ADE) reports as required by 21 CFR 314.80(b) and (c). Specifically, there were 7 potential adverse drug events that were not reviewed or reported to the FDA. These 7 events are as follows:

CASE ID	Product Name	Nature of Inquiry
03/C/012	Naproxen	Lack of effect
03/C/013	Naproxen	Bruising/thinning of skin
03/C/014	HCTZ	Nausea, diarrhea

CASE ID	Product Name	Nature of Inquiry
03/C/018	Propylthiouracil	Elective abortion/fetal malformation
03/C/017	Propylthiouracil	Diffuse alveolar hemorrhage
03/C/015	Atenolol	Increased heart rate
03/C/016	Atenolol	Hair loss

2. Failure to submit a 15 day report to the FDA in violation of 21 CFR 314.80 (c). Specially, your firm received an adverse event for Amoxicillin capsules (Complaint 01/C/040) on September 14, 2001. This report was evaluated as a 15-day report and submitted by your firm to the Medical Controls Agency in the UK, but it was not submitted to the FDA.

3. Failure to submit annual periodic adverse drug reports for 86 drug applications that you purchased from ESI/Lederle on December 28, 2001 and from Mova Pharmaceuticals on January 1, 2002, as required by 21 CFR 314.80 (c)(2)(i). Some of these drug products include, but are not limited to, the following:

Drug Product	Application Number
Acyclovir	74-872
Atenolol	73-543
Diazepam	70-228
Estradiol	40-275
Verapamil	71-881

4. In addition, there has been no documented review and maintenance of the adverse drug event records related to these applications as required by 21 CFR 314.80 (i). Although Mova and Lederle transferred 86 applications to your firm during the period from 12/28/01 to 1/1/02, you have not received, reviewed or filed, any documentation connected to these applications, such as periodic reports.

5. Failure to develop adequate written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experience to FDA, as required by 21 CFR 314.80 (b).

For example, although you have a professional services agreement with [ ] that has been in place since August 20, 2002, adequate operating procedures regarding the exchange of information with this firm have not been established.

No procedures have been established for the medical evaluation of post marketing adverse experiences.

In addition, there is no documented explanation for the delay in logging in complaints once they are received at the facility. For example, your firm received complaint 02/C/077 on August 30, 2002 but it was not logged into your complaint system until the 18th of September 2002.

Neither the above list of deviations nor the Form FDA 483 "Inspectional Observations", which was presented to and discussed with [ ] Director of Technical Operations at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and its regulations. The FDA expects drug manufacturers to establish reasonable mechanisms to assure that all adverse drug experiences are recorded, evaluated and submitted to the FDA within established timeframes as required under 21 CFR 314.80.

We acknowledge receipt of the March 12, 2003 letter from [ ] Director of Technical Operations, containing responses to the February 14, 2003 FDA 483, Inspectional Observations, issued to your firm. Although the corrective actions you outline for FDA 483 points 2, 4 and 5 appear adequate, we feel your responses to points 1 and 3 are inadequate and need further clarification.

In regards to FDA 483 point 1, seven potential ADEs were uncovered during this inspection that were neither reviewed nor submitted to the FDA. In your response letter, you detailed the actions you have taken regarding three of these ADEs. Please forward what actions you have, or will be taking in terms of the remaining four reports.

In addition, in your response to FDA 483 point 3, you stated that you would be submitting the overdue periodic reports to the Agency in a phased in process that will take approximately 240 days. We recommend that you submit a letter to the FDA for each application with an overdue periodic report. This letter should outline the reason for the delay in submitting these periodic reports and the steps you plan to take to insure that these periodic reports, and the next regularly scheduled periodic reports for these applications, will be submitted to the FDA in a timely manner.

We want to re-emphasize that inadequate standard operating procedures for the handling of adverse drug experiences (ADEs) may be the basis for the ADE violations that were uncovered during the inspection of your firm. In particular, we have concerns regarding the exchange of safety data between your firm and your contract research organization, [ ] During this inspection it was revealed that [ ] of your firm had recently conducted an audit of [ ] As a result of this audit, you revised your ADE reporting standard operating procedures, so that will handle ADEs for the drug [ ] only, and will now forward all other ADEs to Clonmel. We are requesting that you provide us with assurance that all ADEs received by [ ] prior to your audit and SOP revisions, were reviewed, evaluated and reported to the FDA.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include but are not limited to seizure and/or injunction. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

We request that you reply in writing within 15 working days of receipt of this letter. Your reply should be sent to the Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Office of Compliance, 11919 Rockville Pike, Rockville, Maryland, 20852, HFD-330, Attn: Denis Mackey.

Sincerely yours,

Kathy P. Miracco

Kathy P. Miracco
Acting Director
Division of Compliance Risk
Management and Surveillance

Enclosure: Form FDA 483, dated February 14, 2003